A SUCCESFULL COMBINATION THERAPY WITH TAGRAXOFUSP-ERZ PLUS VENETOCLAX FOR A PEDIATRIC CASE OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM BRIDGING TO TRANSPLANT

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To the editor;

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy derived from a specific subset of dendritic cells involving skin, bone marrow and other lymphoid organs. To date both acute lymphoblastic and myeloblastic leukemia treatment regimens and FLAG-IDA and hyper CYVAD regimens have been tried but nonetheless disease free survival is low. Tagraxofusp-erz is an FDA approved recombinant cytotoxin as the first CD123-targeted agent ever approved for BPDCN (1). Another agent; Venetoclax, a bcl-2 inhibitor, is being used for relapsed – refractory AML and there are encouraging results as BPDCN survival depends on anti-apopitotic activity protein bcl-2 which was shown in recent studies (2). Here we presented a pediatric case with recurrent BPDCN, first pediatric case of combination therapy with tagraxofusp plus venetoclax and azacitidine plus venetoclax for BPDCN.

CASE:

15 years old, male patient was diagnosed BPDCN in January 2019 with generalized lymphadenopathy and maculopapular skin rash on trunk. AML BFM 2013 was given but one month after last cycle, he relapsed with macular rash. BPDCN was confirmed, Patient was treated with two cycles of FLAG-IDA and a cycle of Hyper-CYVAD regimens, no remission obtained. Tagraxofusp-erzs was planned but patient had COVID-19 pneumonia with no worsening of his ECOG score. Venetoclax initiated 100 mg/day and increased to 400

mg/day in a week, no toxicity and no tumor lysis syndrome was occurred. In combination first cycle of tagraxofusp- erz was given at a dose of 12 mcg/kg/day/5 days. A reversible moderate hepatotoxicity and myelosuppression occurred. There was no sign of capillary leak syndrome which is the most serious and not so rare side effect. On the second day of second cycle, capillary leak syndrome was diagnosed with sudden weight gain, fluid retention, hypoalbuminemia and slight hypotension. Therapy was ceased. Patient recovered with the supportive treatment including inotropic agent within 5 days. Responses after chemotherapy and side effects are outlined at Table -1 and supplemental Table S1.

The patient admitted to stem cell transplantation unit on July 2020 with remission. Myeloablative regimen was busulfan, melphalan and cyclophosphamide. Neutrophile engraftment occured on 10 th day of transplant. He followed for six months in remission. At 6 th month of transplant BPDCN blasts were positive for both bone marrow and central nervous system. Patient was considered ineligible for intensive chemotherapy and repeated tagraxofusp-erz due to lack of experience in relapsed cases and previous capillary leak syndrome side effect. Azacitidine plus venetoclax combination which was shown to be effective in AML for elderly (3) was considered safe rather than standard chemotherapy. Azacitidine was given 100 mg/m2/day for five days sc and oral venetoclax 400 mg/day. He had no response and died.

DISCUSSION:

Pediatric cases of BPDCN has been defined increasingly since 2008 with the report of World Health Organization as a part of AML(4). But lack of experience effects proper diagnosis and optimal treatment.

In 2010, Jegalian et al defined diagnostic features and clinical implications for children and they concluded that BPDCN is less aggressive for pediatric age group and high risk ALL chemotherapy is effective for treatment. Furthermore stem cell transplantation can be a choice in second complete remission(5). In adults; stem cell transplantation is being used as a consolidation therapy due to aggressiveness of the disease(6). Later than, skin involvement was defined as an indicative finding for aggressiveness of the disease in children(7). There is still no consensus about the curative treatment of BPDCN in children.

Tagraxofusp-erz is a recombinant cytotoxin consisting human IL-3 fused to a truncated diphteria toxin and approved for BPDCN (for patients age above 2 years and older) since December 2019. (1,8). There are a handful of pediatric patients who were treated with tagraxofusp-erzs in literature and our patient had treatment for two cycles and reached a remission and a bridge to stem cell transplantation. To obtain remission, we also preferred to add a bcl-2 inhibitor; venetoclax with potential benefit for remission which was successfully applied in literature to a 77 years old patient with comorbidities without significant adverse effect(9). The literature emphasize the risk of transient remission for both adults and children yet for patients in second remission, tagraxofusp is advised as an optimal therapy to decrease residual disease and bridge to stem cell transplantation(6).

Our patient had relapsed six months after stem cell transplantation. Considering previous toxicities, therapy changed to a venetoclax and azacytidine combination treatment notified with efficacy and a very favorable toxicity profile in literature(10). Despite encouraging results no benefit was obtained.

CONCLUSION:

Relapsed/refractory BPCDN has limited therapeutic options and an overall dismal outcome. Conventional therapies have shown to be beneficial but transient remission forced to undergo allogeneic stem cell transplantation. Targeted therapy in combination with bcl-2 inhibitor molecule or demethylating agents are promising but rarity of the disease is an obstacle for prospective studies. Data for BPDCN treatment is extremely limited in pediatric age group. This is the first case report for combination molecular targeted therapies which can be safe and well tolerated options for difficult to treat, chemoresistant patients.

CONFLICTS OF INTEREST:

No potential competing interest was declared by the authors

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